Applicants traverse the rejection. Applicants submit that Wain-Hobson et al. is unnecessary to enable the claimed invention. Applicants further submit that the Wain-Hobson et al. reference serves only as objective evidence of the truth of applicants' assertions regarding the claimed restriction fragments.

1. The specification teaches one skilled in the art that the claimed restriction fragments encode HIV-1 antigens.

The specification teaches one skilled in the art how to synthesize cDNA from HIV-1 virions. (Specification, pages 5-6.) The specification teaches how to clone these cDNA sequences. (Id., pages 6-7.) The specification teaches that the cDNA clone pLAV13 hybridizes to genomic viral RNA and RNA from a variety of infected, but not uninfected, sources. (Id., pages 7-8.) The probe also detected viral DNA in infected, but not uninfected, sources. (Id., page 8.) The specification teaches that, since pLAV13 was primed with oligo-dT, the clone must contain the R, U3, and 3' end of the coding region of HIV-1. (Id., page 8.) The specification teaches one skilled in the art sequencing of HIV-1 clones. (Id., page 7 and Figure 1.) Sequencing of a 50 base pair terminal fragment demonstrated the presence of sequences corresponding to polyA tail within the pLAV13 clone. (Id., page 7 and Figure 1.) Therefore, the identification of a HindIII site proximal to the polyA tail was indicative that this HindIII site was within the R region (i.e. repeat region) of the virus. (Id., page 8 and Figure 1.) Since a retrovirus has two R regions, both preceding and following the coding region, partial HindIII digestion was used to generate a genomic DNA library from infected cells. (Id., pages 8-9.) The DNA was further fractionated to

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enrich for genomic sized DNA fragments. (Id., page 9.) pLAV13 was used as a probe to identify the λ-J19 and λ-J81 clones. (Id., page 9.) Restriction/hybridization analysis of the λ-J19 and λ-J81 clones indicated that these clones were of the expected size for **complete** clones of HIV. (Id., pages 9-11 and Figure 2.) Since the λ-J19 and λ-J81 clones were derived from an *in vitro* infection with an HIV-1 isolate, one skilled in the art expects that these full-length clones will be representative of the genomes of infectious virus. One skilled in the art further expects that the genome of an infectious virus will encode all of the proteins of the virus isolate that was used for infection.

Furthermore, the hybridization of pLAV13 to the 5' and 3' ends of both the λ-J19 and λ-J81 clones indicated that both of these clones contain R sequences at **both** ends of the clones. One skilled in the art recognizes that a genomic clone, of apparently full length size and containing **both** R sequences, is expected to have all of the sequences encoding Gag, Pol, and Env antigens of that retrovirus.

Two distinct clones are disclosed in the specification. (Specification, page 9-11.) Both of these clones demonstrate a similar size of approximately 9kb, have similar restriction enzyme site distributions, and hybridize to pLAV13 at the 5' end. (Specification, Figure 2.) Therefore, the skilled artisan expects that these clones are genomic clones of HIV-1 that encode Gag, Pol, and Env antigens and expects that these clones possess three large open reading frames encoding these antigens within the sequences of the λ-J19 and λ-J81 clones.

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Based on a total genome size of approximately 9000 nucleotides, one skilled in the art expects that Gag, Pol, and Env antigens of HIV-1 will be included within the nucleotides taught in the specification (from approximately 800-3500, 3500-6500, and 6100-9150, respectively). The accuracy of these expectations is validated in the Wain-Hobson et al. reference in Figure 2.

2. The specification teaches one skilled in the art methods to express HIV-1 antigens without the sequence of the λ-J19 clone.

The specification teaches the production of the Gag, Pol, and Env antigens of HIV encoded by the claimed restriction fragments. (Specification, page 13-14.) The skilled artisan is taught a method for identifying genes within subcloned fragments of the λ-J19 clone by cloning fragments of this clone into prokaryotic expression vectors and screening the recombinants with antibodies against HIV-1 antigens. (Id., page 13, lines 28-33.) One skilled in the art recognizes that AIDS patient sera can be used as a source of such antibodies and that a wide variety of expression vectors could be used to express antigens of HIV encoded by all three sense reading frames. The specification teaches the sense and antisense orientation of the λ-J19 clone. (Id., Figure 2.) One skilled in the art recognizes that the subcloning could be performed in a directional manner so as to only express the sense reading frames of HIV-1. One skilled in the art would expect that subclones of the λ-J19 clone would express HIV antigens. Although not all subclones would express HIV-1 antigens, only routine experimentation using the guidance provided by the specification would be required to select those clones which expressed HIV-1 antigens. The specification also teaches that the claimed antigens can be expressed in bacteria,

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yeast, or mammalian cells and the proteins purified. (Specification, page 13, lines 25-27.) The generation of antibodies against the antigens would likewise require only routine experimentation. Accordingly, enablement of the recited claims does not require the sequence of the λ-J19 clone.

The Office states that the availability of the complete nucleotide sequence of the λ-J19 clone would enable the skilled artisan to produce viral antigens from the claimed restriction fragments. (Paper No. 36 at 2, first paragraph.) Applicants submit that the λ-J19 clone enables the expression of the antigens encoded by the nucleotide sequence of this clone, absent evidence to the contrary. Applicants further submit that the λ-J19 clone and the claimed restriction fragments are presumed to encode HIV-1 antigens, absent evidence to the contrary. Therefore, the specification enables the skilled artisan to express specific HIV-1 antigens using the λ-J19 clone by isolating restriction fragments from the λ-J19 clone and cloning them into commercially available expression vectors. This differs from the expression of specific nucleotidic sequences coding for specific antigens characterized by the sequence of the genome, and does not require the nucleotide sequence of the λ-J19 clone.

3. There is no reason to doubt the objective truth of the applicants assertions that the claimed restriction fragments encode HIV-1 antigens.

The claims of the instant invention recite a method of producing antibodies to antigens of HIV-1 using the claimed fragments. The specification teaches that these fragments encode viral antigens. (Specification, pages 4-5 and 13-14.) The specification further teaches that Gag, Pol, and Env antigens of HIV-1 will be included within the nucleotides taught in the specification

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(from approximately 800-3500, 3500-6500, and 6100-9150, respectively). (Specification, pages 4-5.)

> A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied upon for enabling support.

(M.P.E.P. 2164.04.)

Applicants submit that the Office has not presented any reason to doubt the objective truth of the specification. Applicants asserted that the claimed fragments produce HIV-1 antigens. In fact, the sequencing of the λ-J19 clone demonstrated that these assertions were correct. (Wain-Hobson et al., Figure 2.) Therefore, Wain-Hobson et al. provides objective evidence that the claimed fragments encode HIV-1 antigens.

The Office states that the availability of the complete nucleotide sequence of the λ-J19 clone is required to enable the skilled artisan to produce viral antigens from the claimed restriction fragments. (Paper No. 36 at 2, first paragraph.) However, applicants respectfully disagree. Wain-Hobson et al. is not cited to enable the claimed invention with respect to the earlier priority date. **Rather, Wain-Hobson et al. merely validates the correct assertions of the applicants.** Accordingly, unless the Office can provide some reasons to doubt the truth of the applicants' assertions and objective evidence in support of these assertions, the specification must be taken as enabled, which entitles applicants to the earlier filing date of September 19, 1984.

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4. Wain-Hobson et al. is not prior art.

As previously submitted in the Amendment in response to paper No. 4, dated February 9, 1994, the disclosure of the instant application is identical to the priority document UK 84 23659, filed September 19, 1984. (Amendment, page 8.) Therefore, a claim to this priority date is appropriate. This priority date precedes that of the Wain-Hobson et al. reference of January 1995. Accordingly, applicants respectfully request withdrawal of the rejection.

For the foregoing reasons, applicants believe that this application is now in condition for allowance. In the event the Examiner disagrees, he is invited to call the undersigned to discuss the remaining issues.

If there are any other fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 06-0916. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested, and the fee should also be charged to our Deposit Account.

Respectfully submitted,

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By: _____
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Dated: December 1, 1997

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